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SHORT REPORT



WILEY

A homozygous stop gain mutation in *BOD1* gene in a Lebanese patient with syndromic intellectual disability

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Abstract

Intellectual disability (ID) is a neurodevelopmental disorder characterized by limitations in both intellectual and behavioral functioning. It can occur in non-syndromic and syndromic forms involving multiple organs. While the majority of genetic variants linked to ID are de novo, inherited variants are also detected in some forms. Here, we report a consanguineous Lebanese family presenting with an autosomal recessive syndromic ID characterized by neurodevelopmental delay, mild dysmorphic features, hearing impairment and endocrine dysfunction. Whole exome sequencing enabled the detection of the homozygous nonsense mutation in *BOD1*, p.R151X, in the proband. *BOD1* is required for chromosomes biorientation during cell division. It also contributes to the regulation of cell survival and to the modulation of fatty acid metabolism. Another nonsense mutation in *BOD1* was linked to ID in a consanguineous Iranian family. This is the second report of *BOD1* mutations in humans and the first in a syndromic ID including gonadal dysfunction and high-frequency hearing impairment. Our findings confirm the involvement of *BOD1* in cognitive functioning and expand the clinical spectrum of *BOD1* deficiency.

KEYWORDS

consanguinity, gonadal dysfunction, syndromic intellectual disability, whole exome sequencing

1 | BACKGROUND

Intellectual disability (ID) is a neurodevelopmental disorder characterized by limitations in intellectual functioning assessed by the Intelligence Quotient (IQ) and in adaptive behaviors.¹ It affects 1 to 3% of the general population.² Mild, moderate, severe, and profound are terms commonly used to define the severity of the disease.³ In parallel, ID disorders are grouped into non-syndromic or syndromic ID where patients show additional clinical signs such as dysmorphic features, skeletal and/or

metabolic defects.⁴ While environmental factors can lead to non-syndromic ID,^{5,6} a genetic etiology is thought to be present in 15% to 62% of ID cases,^{7,8} especially in severe forms.⁹ The majority of genetic variants linked to severe ID are de novo.^{7,8,10} However, inherited variants are also detected in autosomal dominant and recessive ID disorders.^{11,12} Chromosomal aberrations and copy number variations account for about 15% of ID cases.^{7,8} Pathogenic SNVs (Single Nucleotide Variations), occurring in coding genomic regions are responsible for more than 50% of ID cases. Pathogenic non-coding SNVs regulating gene expression may also lead to ID.^{7,8} Therefore, diagnostic yield of whole genome sequencing in patients with ID can reach 62%.⁸ Nevertheless, the molecular basis of several ID disorders remains unelucidated.

Here we report a homozygous nonsense mutation in *BOD1* in a consanguineous Lebanese family presenting a syndromic form of

Abbreviations: AAIDD, American Association on Intellectual and Developmental Disabilities; CADD, combined annotation dependent depletion; DSM, diagnostic and statistical manual of mental disorders; ExAC, exome aggregation consortium; ID, intellectual disability; IQ, intelligence quotient; MAF, minor allele frequency; OFC, occipital head circumference; SD, standard deviation; SNV, single nucleotide variation; WES, whole exome sequencing.

Nadine Hamdan and Cybel Mehawej are joint first co-authors.

ID. This is the second report of *BOD1* mutations in humans and the first in syndromic ID including gonadal dysfunction and high-frequency hearing impairment.

2 | MATERIAL AND METHODS

2.1 | Patients

A 14-year-old affected boy, born to a consanguineous Lebanese family is reported in this study. A history of two miscarriages existed in the family. Pregnancy and delivery were normal. Physical examination at birth demonstrated normal weight, height and occipital head circumference (OFC). There was no history of postnatal infection or trauma. Severe myopia and signs of psychomotor delay started to show on the patient at 1 year of age.

At the age of 9 years, he was diagnosed with syndromic ID including short stature (-2 SD), mild dysmorphic features, high-frequency hearing impairment (Figure 1), obesity, endocrine dysfunction and micropenis with cryptorchidism. Dysmorphic features included: microcephaly (OFC = 52 cm, 35th centile), strabismus, ear lobes deformities, short neck, small hands (13 cm, <3rd centile) and small feet. The neurodevelopmental delay in the patient consisted in limitations in both behavioral and intellectual functioning (with an IQ of 44), speech delay, attention deficit and learning difficulties. Endocrine dysfunction was mainly defined by Hypogonadotropic hypogonadism and short stature including 20 months of bone age delay. Brain magnetic resonance imaging, electroencephalography and thyroid function evaluation were normal.

Parents also reported that the proband has an uncle presenting ID, dysmorphic features, short stature, plethoric obesity, small hands,

ear malformations as well as attention deficit, learning difficulties and hypogonadism. However, further evaluation of this patient was not possible because he refused to participate in this study.

2.2 | Isolation of genomic DNA

Written informed consent was obtained from the parents for study enrollment and publication. DNA was extracted from peripheral blood by standard methods.¹³

2.3 | Whole exome sequencing (WES)

Sequences were captured and enriched using Agilent SureSelect Human All Exon kit version 5.0. Samples were then multiplexed and sequenced on an Illumina HiSeq 2500 PE100-125. FASTQ files were aligned to the hg19/b37 reference genome using the Burrows-Wheeler Aligner (BWA) package version v0.6.1.¹⁴ Variant calling was performed using the Genome Analysis Tool Kit (GATK)¹⁵ version 3.3, then annotated with VarAFT 1.61.¹⁷ Variants were filtered for protein-altering variants, including truncating variants, canonical splice-site variants and missense variants, based on their frequency in dbSNPv137 (<1%), ExAC/gnomAD v2.11 (<1%) and our *in-house* database (<1%).

2.4 | Sanger sequencing

Selected variants were studied in the proband, his parents and two of his unaffected siblings by Sanger sequencing.

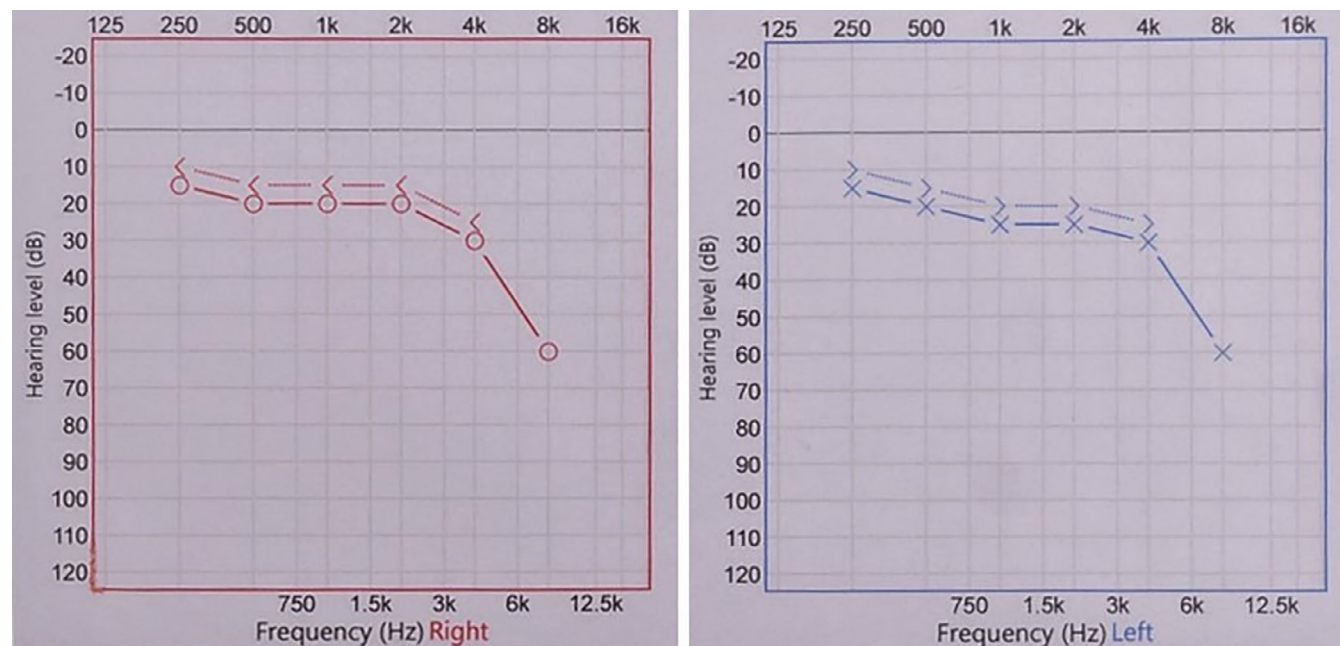


FIGURE 1 Audiograms showing high-frequency hearing impairment in the proband [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

WES was performed on the proband DNA. Data was first filtered for rare protein-altering variants including canonical splice-site variants. Then, assuming an autosomal recessive condition occurring in a consanguineous family, we selected homozygous variants. This led to the identification of 17 variants in different genes (Table 1) of which six are associated with diseases in human. Among these, *NCAPG2* and *BOD1* were selected as candidate based on the clinical manifestation of the patient. Sanger sequencing allowed the exclusion of the *NCAPG2* variant that was homozygous in one of the unaffected sibling and the selection of the nonsense mutation in *BOD1* (NM_138369: c.451C>T; p.R151*) that segregated with the disease in the family (Figure 2). This variant is absent in our local database, found at very low frequency at a heterozygous state in ExAC (minor allele frequency of 0.0000159) and has a CADD (Combined Annotation Dependent Depletion) score of 39, suggesting that it is pathogenic.

In parallel, heterozygous variants in genes known to be linked to autosomal dominant neurodevelopmental disorders were ruled out by a targeted analysis of WES data.

4 | DISCUSSION

Here, we report a homozygous nonsense mutation in *BOD1* in a consanguineous Lebanese patient with a syndromic form of ID, including gonadal dysfunction and high-frequency hearing impairment. *BOD1* (Biorientation of chromosomes in cell division 1) is required for chromosomes biorientation during cell division.¹⁶ It is localized at kinetochores from prometaphase until anaphase¹⁶ where it inhibits the phosphatase 2A, thus regulating cell cycle progression.^{17,18} A homozygous nonsense mutation in *BOD1* (NM_138369: c.334C>T; p.R112*) was previously observed in four female siblings of a consanguineous Iranian family, suffering from mild to moderate ID. Reported patients also presented primary or secondary amenorrhea of unknown cause occurring in the absence of endocrine dysregulation.¹⁹ The identification of a novel nonsense mutation in *BOD1* in the family reported herein expands the clinical spectrum of *BOD1* deficiency and links the gene to a syndromic ID including a gonadal dysfunction, dysmorphic features and moderate hearing impairment. Further to the involvement of *BOD1* in cell cycle regulation, this protein plays an important role in post mitotic neurons where it contributes to the development and maintenance of cognitive features.¹⁹ It also modulates fatty acid metabolism that is mediated by its interaction with the histone lysine methyltransferase SET1B.

TABLE 1 List of the homozygous identified variants by WES analysis

Gene	Linked to a human disease	Reference	Variation	CADD_phred score	MAF in gnomAD	Varsome prediction
<i>EME2</i>	NA	NM_001257370.1	c.7C>T (p.Arg3Trp)	23.9	-	Uncertain Significance
<i>MYOM3</i>	NA	NM_152372.4	c.3934G>C (p.Ala1312Pro)	33	-	Uncertain Significance
<i>ZNF638</i>	NA	NM_001014972.2	c.1538A>G (p.His513Arg)	0.012	0.0003	Likely Benign
<i>DOK5</i>	NA	NM_018431.5	c.353A>G (p.Asp118Gly)	23.1	0.0001	Uncertain Significance
<i>CEP55</i>	Hydranencephaly with renal aplasia-dysplasia	NM_001127182.2	c.641A>G (p.His214Arg)	10.07	0.0001	Likely Benign
<i>XYLT2</i>	Spondyloocular syndrome	NM_022167.4	c.128C>A (p.Ala43Glu)	23.1		Likely Benign
<i>NCAPG2</i>	Khan-Khan-Katsanis syndrome	NM_017760.7	c.2456C>T (p.Pro819Leu)	13.3	9.70E-05	Likely Benign
<i>BOD1</i>	Intellectual disability	NM_138369.3	c.451C>T (p.Arg151Ter)	39	-	Uncertain Significance
<i>MKI67</i>	NA	NM_002417.5	c.8042G>A (p.Gly2681Asp)	21.5	-	Likely Benign
<i>SATL1</i>	NA	NM_001012980.2	c.1750G>A (p.Val584Ile)	16.46	-	Uncertain Significance
<i>MZT2B</i>	NA	NM_025029.5	c.148G>A (p.Ala50Thr)	13.43	-	Uncertain Significance
<i>TPP2</i>	Sterile brain malformation mimicking multiple sclerosis	NM_003291.4	c.1270A>G (p.Ile424Val)	10.38	6.46E-05	Likely Benign
<i>PHPT1</i>	NA	NM_001287343.2	c.331A>G (p.Ile111Val)	2.165	-	Likely Benign
<i>C2CD6</i>	NA	NM_001168221.2	c.4783C>T (p.Gln1595Ter)	37	-	Uncertain Significance
<i>RPS11</i>	NA	NM_001015.5	c.39G>C (p.Gln13His)	27.6	-	Uncertain Significance
<i>MMEL1</i>	NA	NM_033467.4	c.1366G>A (p.Val456Ile)	19.62	0.0002	Likely Benign
<i>ANTXR1</i>	GAPO syndrome	NM_032208.2	c.1312C>T (p.Arg438Cys)	32	0.0003	Uncertain Significance

Abbreviations: CADD, combined annotation dependent depletion; MAF, minor allele frequency; NA, not available.

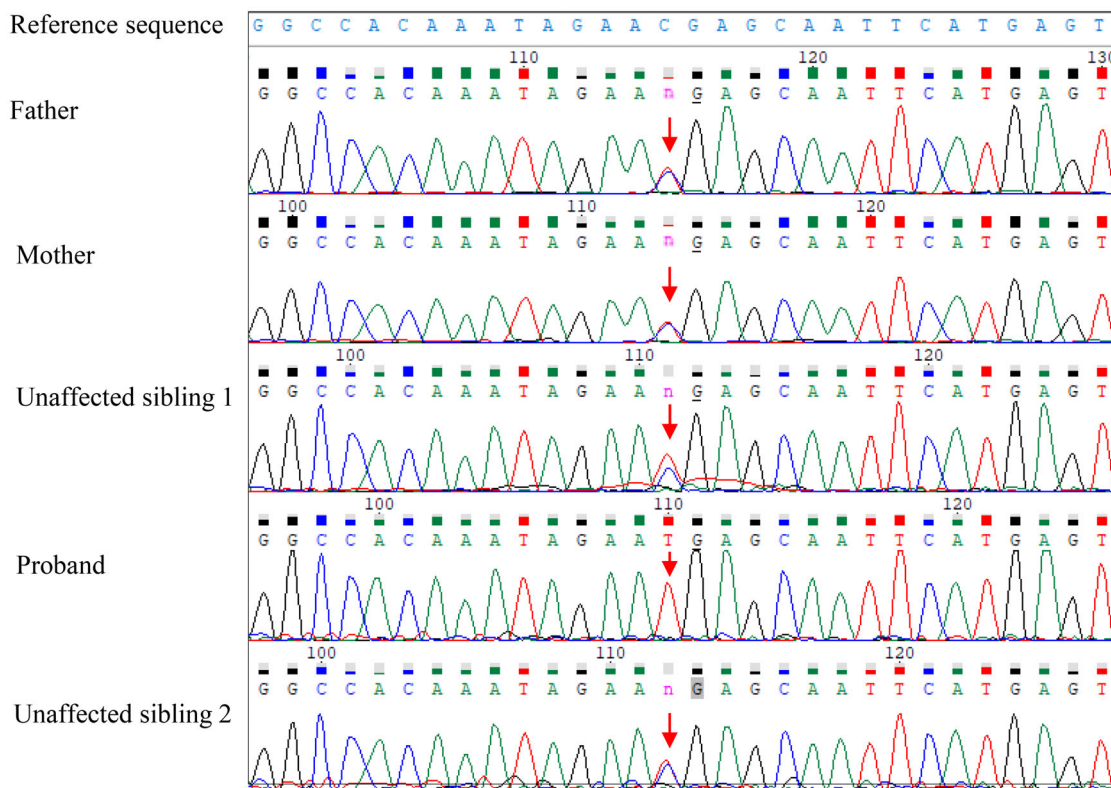


FIGURE 2 Chromatograms showing the segregation of the p.R151* mutation in *BOD1* in the family. The mutation is indicated by the red arrow. n: heterozygous peak [Colour figure can be viewed at wileyonlinelibrary.com]

Indeed, *BOD1* is a cytoplasmic-specific subunit of COMPASS, a complex of proteins associated with Set1.²⁰ Interestingly, de novo mutations in *SETD1B* encoding SET1B, are associated with syndromic ID, epilepsy and autism.²¹ Given that *BOD1* stabilizes SET1B and is essential for its activity,²⁰ we propose that the cognitive impairment associated with *BOD1* deficiency might be mediated by SET1B. In parallel, loss of SET1B or *BOD1* induces the upregulation of adiponectin receptor 1 (AdipoR1) and activation of its signaling pathway.²⁰ Adiponectin, an adipose tissue-derived hormone, links the regulation of metabolic homeostasis with reproductive processes.²² AdipoR1 is expressed in hypothalamic-pituitary-gonadal axis and its activation regulates the expression and/or secretion of Kiss, gonadotropin-releasing hormone and gonadotropin. Adiponectin plays essential roles in fertility; from gametogenesis to gestation. It also contributes to embryo development.²³ This suggests that the modulation of adiponectin signaling pathways by *BOD1* deficiency might be responsible for the gonadal disorder of our patients and for the amenorrhea in the reported Iranian family.¹⁹

Last but not least, while complete loss of *Bod1* in mice is lethal, heterozygous carriers of the *Bod1* knock-out allele show hearing impairment at high frequencies.²⁴ This phenotype is interestingly observed in the proband and not seen in any of his unaffected siblings, thus suggesting its possible link with *BOD1* deficiency. Unfortunately, hearing performance was not assessed in the Iranian family.¹⁹ Reporting further cases with *BOD1* deficiency is crucial to better delineate the spectrum of this disease.

Here, we report a novel homozygous nonsense mutation in *BOD1* in a consanguineous Lebanese patient with ID syndromic form. This is the second report of *BOD1* mutations in humans and the first associated with syndromic ID including gonadal dysfunction and high-frequency hearing impairment. Our findings confirm the involvement of *BOD1* in cognitive development and expand the clinical spectrum of the disease linked to a mutation in this gene. Further functional studies in murine models are also essential for the elucidation of the pathogenic mechanisms of *BOD1* deficiency.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Nadine Hamdan, Cybel Mehawej, and Eliane Chouery wrote the manuscript. Nadine Hamdan, Nadine Jalkh and Cybel Mehawej performed data analysis. Cybel Mehawej, O De Backer, and Eliane Chouery conceived, designed the study. Sandra Corbani and Joelle Abou-Ghoch conducted the experiments. Nadine Jalkh conducted

WES bioinformatics analysis. Ghada Sebaaly performed the clinical investigation of the patients.

ETHICS STATEMENT

Approval to conduct the study was obtained from the Ethics Committee of Saint Joseph University, Beirut, Lebanon. Parents signed an informed consent for data publication.

DATA AVAILABILITY STATEMENT

Data analyzed during this study are included in this published article. Raw data is available upon request.

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